EXHIBIT A192

Perineal talc use and ovarian cancer: a critical review

Joshua E. Muscat[a,b] and Michael S. Huncharek[b,c]

Talc, like asbestos, is a silicate that has been studied in relation to cancer risk. Several studies conducted over the past 25 years found an association between perineal talc powders and ovarian cancer. The summary relative risk is about 1.3 (95% confidence intervals 1.2–1.5) and these data have been interpreted as supporting a causal role. In this review article, we discuss the chemical and morphological features of talc and asbestos, and explain why despite their similar chemical classification talc does not possess asbestos-like carcinogenic properties. The heterogeneity in the perineal dusting studies has raised important concerns over the validity of the exposure measurements, and the lack of a consistent dose–response effect limits making causal inferences. Perhaps more importantly, whereas it is unknown whether external talc dust enters the female reproductive tract, measures of internal talc exposure such as talc-dusted diaphragms and latex condoms show no relationship with ovarian cancer risk. In addition, the therapeutic use of high dose cosmetic grade talc for pleurodesis has not been shown to cause cancer in patients receiving these treatment modalities. Talc is not genotoxic. Mechanistic, pathology and animal model studies have not found evidence for a carcinogenic effect. In summary, these data collectively do not indicate that cosmetic talc causes ovarian cancer. *European Journal of Cancer Prevention* 17:139–146 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Department of Health Evaluation Sciences, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, [b]Meta-Analysis Research Group and [c]Division of Preventive Medicine, University of South Carolina School of Medicine Columbia, South Carolina, USA

Correspondence to Joshua E. Muscat, PhD, MPH, Pennsylvania State College of Medicine, 500 University Blvd., Hershey, PA, USA
Tel: +1717 531 4710; e-mail: jmuscat@psu.edu

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Introduction

The association between perineal talc powder dusting and ovarian cancer was determined in 16 case–control studies (Cramer *et al.*, 1982, 1999; Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow and Weiss, 1989; Chen *et al.*, 1992; Harlow *et al.*, 1992; Tzonou *et al.*, 1993; Purdie *et al.*, 1995; Chang and Risch, 1997; Cook *et al.*, 1997; Godard *et al.*, 1998; Rosenblatt *et al.*, 1998; Wong *et al.*, 1999; Ness *et al.*, 2000; Mills *et al.*, 2004) and the Nurses' Health Study (Hankinson *et al.*, 1993; Gertig *et al.*, 2000). The summary relative risk for these studies in a meta-analysis (excluding Mills *et al.*, 2004) is 1.33 [95% confidence intervals (CIs) 1.16–1.45] (Gross and Berg, 1995; Huncharek *et al.*, 2003). Methodological issues such as response rates, validity, reliability, bias, the consistency of dose–response relationships, and causality have been reviewed elsewhere (Muscat and Barish, 1998).

The use of talc-based powders and their possible health effects has received considerable attention in the print media and in authoritative and consumer-oriented websites. The basis for these concerns is the increased risks of ovarian cancer associated with perineal dusting. Despite these concerns, a comprehensive review of the talc literature and the conceptual and scientific understanding of how talc could cause ovarian cancer has not been adequately considered in the medical literature. The current review provides a historical context on the origins of the talc and ovarian cancer hypothesis, how certain assumptions on talc carcinogenicity were not properly understood, and describes findings on numerous other data on talc and cancer besides the perineal dusting associations. We conclude with suggestions for new avenues of research in this area.

Historical development and public awareness of concerns over talc

The chemical similarity between talc and asbestos provided the rationale in the 1970s for suspecting that the practice of perineal dusting with talc-containing powders could cause ovarian cancer in humans. Supporting this hypothesis were findings that asbestos, which is a human lung and pleural carcinogen, induces ovarian tumors in guinea pigs (Graham and Graham, 1967), and limited human data of elevated standardized mortality rates of ovarian cancer in asbestos manufacturing industries (Acheson *et al.*, 1982; Newhouse *et al.*, 1982; Wignall and Fox, 1982). More recent studies have not confirmed an excess occupational risk (Langseth and Kjaerheim, 2004).

The initial public concerns over talc, however, were not due to its inherent properties but findings of silica minerals in samples of commercial body powders in 1978. It was thought that inhaled powder could cause scarring of lung tissue, mesothelioma, or lung cancer (Henderson *et al.*, 1971). About half of the samples contained respirable quartz, a lung carcinogen. No concerns were raised at that time about ovarian cancer, but in 1982 a

case–control study of ovarian cancer that collected information on talc use reported an increased risk with perineal dusting (Cramer *et al.*, 1982). These findings were reported in highly circulated newspapers (Anonymous, 1982a, b) and subsequent domestic production of cosmetic grade talc steadily declined in the next two decades (Kelly and Matos, 2005). Cosmetic grade talc was nominated to the National Toxicology Program's (NTP) 10th Report on Carcinogens, but the decision was deferred for future consideration. In 2006, the International Agency for Research on Cancer listed cosmetic (perineal) talc application as possibly carcinogenic to humans (e.g. group 2B) (Baan *et al.*, 2006).

Minerology of talc and asbestos

Talc and asbestos are both silicate minerals. Minerals are classified according to their anionic structure, and subclasses are defined by chemical composition or structure. Classes and subclasses can be further divided into mineral groups on the basis of atomic structure and chemical similarities. Talc is a magnesium silicate hydroxide, characterized by water molecules trapped between silicate sheets, which belongs to the silicate subclass phyllosilicate and the clay group montmorillonite/smectite. The three other major phyllosilicate clay groups are kaolinite/serpentine, illite, and chlorite.

Asbestos is the generic or commercial name for six naturally occurring fibrous minerals including amosite, chrysotile, crocidolite, which have been used in industrial applications, and the fibrous varieties of tremolite, actinolite, and anthophyllite. Asbestos is morphologically distinct from talc and belongs to different silicate mineral groups and subgroups. The serpentine mineral group includes the asbestiform chrysotile, which is the most abundant variety of the serpentine mineral group. It is distinct from the nonasbestiform serpentines in that its brucite and silicate layers bend into tubes that produce clusters of curled fibers that are often entangled. The fibers are bundled but easily separate out from the host matrix. The inosilicate/amphibole group of minerals is very common in surface rock. Five asbestiform minerals exist in the inosilicate/amphibole group, which differ by chemical composition but all form individual rather than bundled needlelike fibers. All asbestos fibers have a high-tensile strength and are characterized by an aspect ratio (length to diameter) of 20–1000.

The carcinogenic effects of asbestos have been extensively studied and documented in the medical literature (Huncharek, 1986; Mossman and Gee, 1989). It is clear that the morphologic structure of serpentine asbestos and the fibrous form of amphiboles is responsible for their carcinogenic properties, much more than its atomic constituents (Stanton *et al.*, 1977, 1981). In contrast, talc which is a member of the montmorillonite/smectite group, rarely occurs in the asbestiform habit (a mineral's fibrous pattern of growth). Even asbestiform talc is not carcinogenic like asbestos because of its dissimilar chemical and physical properties.

The geological classification of minerals is not straightforward and improvements in analytic techniques have led to changes in the nomenclature over time. Minerals are chemically similar but can have substantially different properties. It was noted with levity that the problem with mineralogical analogies can be appreciated by the fact that calcium carbonate constitutes both a pearl and chalk (Krause and Ashton, 1978). These critical distinctions, however, have not been recognized in the epidemiologic literature.

Proposed mechanisms for talc-induced ovarian cancer

Given the dissimilarities between talc and asbestos with regard to their fibrous shapes, the weak but increased associations in the epidemiologic studies could be attributed to other mechanisms assuming that the statistical associations are unbiased and not due to confounding. Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response (Ness and Cottreau, 1999). Pelvic inflammatory diseases, however, such as endometritis, peritonitis, tubo-ovarian access formation, and salphingo-oophoritis have in general not been associated with an increased risk of ovarian cancer (Risch *et al.*, 1994; Risch and Howe, 1995; Parazzini *et al.*, 1996; Green *et al.*, 1997). A meta-analysis of studies of anti-inflammatory drug use found no reduction in ovarian cancer risk (Bonovas *et al.*, 2005). Inflammation induces pleural fibrosis (Antony, 2003) but the detection of talc particles in human ovarian surgical specimens was not accompanied by fibrosis in one study (Heller *et al.*, 1996b).

It was suggested that the associations between perineal talc dusting and ovarian cancer might be explained by the induction of ANTI-MUC1 antibodies (Cramer *et al.*, 2005). This idea has been debated on statistical grounds where talcum powder applied to the perineum was associated with increased ANTI-MUC1 expression but the correlation was also observed when talc powder was applied to other body parts. More importantly the simple observation that talc elevates immunoglobulin protein levels in blood, possibly via heat shock proteins seems to have no known direct relevance for ovarian cancer since ANTI-MUC1 is associated with other cancers (Muscat *et al.*, 2005) and because there is no known role of heat shock proteins in ovarian cancer risk.

Ecologic data

The domestic sales of cosmetic talc powder in the US declined from 41 000 metric tonnes in 1982 to 5000 metric tonnes in 2004 (Kelly and Matos, 2005). Sales of

other talc products have remained relatively stable indicating that the decline in cosmetic sales is due to decreased demand rather than decreased production capacity. No corresponding temporal decline exists in the reported use of perineal talc powder in the epidemiologic studies of ovarian cancer and this discrepancy has not been addressed. The decline in powder sales may have directly resulted from health concerns over talc resulting from study findings and consumer warnings in the print and electronic media. The weak associations reported in the case–control studies could be explained by an increased awareness about the suspected health hazards from talc among case participants. Alternatively, the decline in sales might be due to temporal changes in feminine hygienic practices, or to demographic changes in population characteristics. We can only speculate about these issues, but the dearth of marketing or epidemiologic data on the characteristics of women who uses talc powders, for what reasons, how they are applied and under what circumstances, and whether these factors have changed over time add to the ambiguities in exposure assessment that is raised by the sales data. Consequently, the question of perineal talc exposure and ovarian cancer risk is only understood from the limited exposure data in case–control studies.

Even this data is somewhat problematic since the terminology used to define exposure varied across studies from 'dusting powders,' 'genital powder,' 'baby powder,' 'talc,' to 'talc (genital/rectal and feet,' 'bath talc,' 'body talc' and 'talc use on perineum).' Some studies did not distinguish talcum powder from talc-free, powders, or the location of application was not specified. Whereas the application was specified, it may not be certain whether the participants understood the meaning of the words perineum or genital.

Issues in the case–control literature of talc dusting

Clinical perspectives of talc exposure assessment

One aspect of the epidemiologic literature to date is that the studies have not incorporated a clinical perspective on exposure assessment. Although many lifestyle exposures can be determined with reasonable accuracy using a structured questionnaire, the highly personal nature of talc use may require a detailed clinical understanding to determine the exact nature of the practice for reducing any possible adverse health effects. The use of genital talc powders could be seasonal and vary by changes in personal history (e.g. changes in marital status, sexual partners, use of contraceptive birth control, parity, occupation, etc.). It is unknown whether individual participants respond differently to questions on genital dusting according to whether undergarments were worn at the time of application, whether dusting occurred before or after sexual intercourse, and whether dusting occurred in combination with douching. The amount of talc introduced into the female genital tract might depend on these hygienic practices, and may vary by lifestyle changes, season, bodyweight, and other factors. A typical lifestyle questionnaire also requests respondents to define their practice into a quantifiable frequency, which forces the study participants to respond into a pattern of regular use that in the case of talc may be unrepresentative of lifetime use, and not reflect cyclical or temporary changes (Muscat and Barish, 1998).

Infant exposure

Epidemiologic studies have not determined whether the internal female genital tract is physically exposed to talc dusts during infancy. Such questions need to consider whether the hymen blocks exposure into the infant genital tract. Clearly, adult women cannot recall their early childhood exposures but the inability to measure this exposure needs to be considered in the overall evaluation of talc carcinogenicity.

Exposure to the adult reproductive tract

Perhaps the most fundamental unanswered question on perineal dusting is whether powder applied to skin surfaces surrounding the external genitalia actually enter the adult female genital tract. It is uncertain whether dusting contaminates the vagina or cervix and if so under what hygienic conditions. The issue of particle retrograde migration from the cervix to the ovaries assumes that talc particles migrate upwards against both gravity and the downward flow of vaginal mucous and menstrual fluids. The limited number of human experimental studies have found evidence for particle migration in the female reproductive tract, although the interpretation of these findings have been debated (Wehner, 2002). For example, one study found that starch particles from surgical gloves migrated from the vagina into the uterine cavity and fallopian tubes in women undergoing subsequent hysterectomy (Sjosten *et al.*, 2004). The tissue particle count was significantly greater than in women treated with nonpowdered gloves. The starch particles, however, were introduced under routine gynecologic examination that involved the use of a speculum, and the mobility of starch might be different than talc owing to its different chemical composition.

Talc particles have been detected in human ovarian surgical specimens. In early studies, it was assumed that the vagina was the route of exposure, although as noted previously occupational studies indicated that inhaled particles could migrate from the lungs to the ovaries. The first study that described the presence of talc particles in ovarian cancer tissue was performed when surgical donning gloves were manufactured with talcum powder or other dusting agents (Henderson *et al.*, 1971). Concerns over contamination led to a second effort that was conducted after manufacturing processes were based

on talc-free products. The initial findings were confirmed and contamination was ruled out as an explanation (Henderson *et al.*, 1979). To further explore these issues, a study of normal ovarian tissue obtained from women undergoing oophorectomy was conducted in relation to reported talc use. Some samples that had no measurable talc counts were obtained from women who reported regular talc dusting, whereas other samples with high concentrations were obtained from women who reported no genital talc use (Heller *et al.*, 1996b). In contrast, the same group reported a correlation between asbestos exposure and asbestos concentrations in ovarian tissue (Heller *et al.*, 1996a). These pathology studies require careful interpretation because of their small sample sizes and limited exposure assessment, but support the notion that ovarian tissue may be contaminated via inhalation and not perineal dusting.

Exposure via diaphragms

Given the uncertainty on whether perineal dusting exposes the internal female genital tract to talc, it seems clinically intuitive that the most valid method for testing the carcinogenic potential of talc is to determine its association with talc-dusted diaphragms or condoms. By definition, the female reproductive tract is exposed to talc-containing powders introduced by diaphragms, whereas an exposure route on the basis of perineal dusting requires unproven assumptions about vaginal exposure. The data on talc-dusted contraceptive diaphragms is less extensive than that for talc dusting, but a recent meta-analysis of nine case–control studies found a summary odds ratio of 1.03 (95% CI: 0.80–1.33) (Huncharek *et al.*, 2007). These results suggest that cosmetic talc is not associated with ovarian cancer risk. As with the talc dusting data, the validity of the diaphragm data has not been determined as little is known about the application of talc in female hygienic practices. For example, diaphragms may be used with contraceptive jelly that could potentially inhibit or facilitate the migration of talc into the uterus. The observational studies of ovarian cancer did not collect or report information on the frequency and duration of this practice, but it was acknowledged in one study that the lack of a positive association with talc-dusted diaphragms led to the exclusion of this particular measure in a follow-up study (Cramer *et al.*, 1999). From an epidemiologic perspective it may be argued that the diaphragm and condom data is more valid if not the only valid measure of female reproductive tract talc exposure.

Exposure via barrier condoms

A similar argument may be made for talc-dusted condoms. In seven studies that gathered information on condom use, none of these including the Nurses Health Study found an increased risk with ovarian cancer (Table 1). Information on frequency and duration of use was not collected in these studies. Latex condoms have been manufactured with a wide variety of dusting powders including talc, starch, silica, and other minerals. The density of talc particles differs substantially by brands (Kasper and Chandler, 1995). Condom sales increased substantially in 1975, rising by about 10% annually until 1980 (Castleman, 1980). Similarly, the use of condoms was reported to increase significantly by consumers in the National Surveys of Family Growth, that is from 13% in 1988 to 19% in 1995 in women (Piccinino and Mosher, 1998; Bankole *et al.*, 1999). This increase was attributed to a greater awareness of the health risks associated with older formulations of oral contraceptives and protection against sexually transmitted diseases including HIV infection. It was predicted in 1995 that the increase in condom use would increase the incidence of ovarian cancer in the United States if the talc in condoms was carcinogenic (Kasper and Chandler, 1995). The annual −0.9% decline in the age-adjusted surveillance, epidemiology and end results incidence of ovarian cancer since 1987 would appear to indicate that talc is not an ovarian carcinogen. Talc has been the preferred dusting powder used to manufacture latex condoms, but since 1995 talc has fallen into disfavor as a dry lubricant and newer products are manufactured with cornstarch.

Asbestos contamination and confounding

Cosmetic talcum powder contains greater than 95–99% pure talc, whereas other dusting powders are typically composed of talc, cornstarch and other additives. Cosmetic grade talc is asbestos-free and has been for several decades, but some baby powders manufactured in the 1970s contained small amounts of tremolite or quartz silica (Rohl *et al.*, 1976). The X-ray analytic methods to

Table 1 Summary of studies with data on latex condom use and ovarian cancer risk

Study	Cases *N* (% exposed)	Controls *N* (% exposed)	Crude relative risk	95% CI
Chen	112 (35.7%)	224 (41.1)	0.79	0.5–1.27
Cook	313 (2.2%)	256 (4.5%)	0.49	0.2–1.17
Cramer	169 (11.2%)	191 (15.7%)	0.68	0.37–1.26
Booth	213 (49.3%)	420 (51.1%)	0.92	0.67–1.29
Hankinson	150 (14%)	NA	0.78	0.49–1.23[a]
Ness	767 (8%)	1367 (9%)	1.0	0.7–1.4
Rosenblatt	72 (48.6%)	43 (51.1%)	0.9	0.42–1.92

Nurses' Cohort data.
[a]The relative risk and 95% confidence interval (CI) are adjusted for age.

determine the concentration of these contaminants have been questioned (Krause, 1977) and the diffraction patterns did not distinguish between fibrous and nonfibrous minerals. In the epidemiologic studies of ovarian cancer that distinguished dates of exposure, the magnitude of the odds ratios for perineal dusting did not vary significantly between early and later exposure periods. The overall odds ratios in these studies was also fairly consistent regardless of whether the studies were conducted during the 1970s or decades later, suggesting that crystalline quartz or other silicates in talc powder were not confounders.

Clinical detection, treatment and management of ovarian cancer

Ovarian cancer ordinarily presents with few distinctive symptoms. The most common indication of ovarian cancer is ascites, which is excess fluid accumulation in the abdomen that causes abdominal swelling. Other indications include abdominal/pelvic discomfort or pressure, back or leg pain, bloating, changes in bowel function or urinary frequency, fatigue, gastrointestinal problems, malnourishment, jaundice, anemia, nausea, or loss of appetite and menorrhagia or excess vaginal bleeding. Menorrhagia is menstruation with excessive flow and duration and is a common complaint in premenopausal women. The World Health Organization reported that 18 million women aged 30–55 years perceive their menstrual bleeding to be exorbitant but that only 10% of these women experience blood loss severe enough to be defined clinically as menorrhagia. In a study of 187 patients with ovarian carcinoma, 24% reported excessive vaginal bleeding or menorrhagia (Munnell, 1952), a symptom that might lead to a temporary increase in talc use. A recent review found that vaginal bleeding was one of the most reported symptoms of ovarian cancer (Bankhead *et al.*, 2005).

Meta-analysis uncovers heterogeneity in studies and is a powerful tool for exploring possible biases, particularly as it does not rely on subjective assumptions about study quality. A meta-analysis of the talc dusting studies showed that risk estimates varied by study design (e.g. hospital vs. population based) (Huncharek *et al.*, 2003). The relative risk was 1.38 (1.25–1.52) for population-based studies and 1.19 (0.99–1.41) for hospital-based studies. Conventional wisdom suggests that this difference is due to a nonrepresentative exposure rate in hospital controls, and that the results from population-based studies are more accurate. The proportion of controls dusting with talc powder, however, was the same in both groups, that is 32%. One explanation is that case participants in population-based studies had the opportunity to review literature about the causes of ovarian cancer after discharge but before the interview, whereas hospital-based participants did not have this opportunity. Additionally, clinicians may recognize a 'treatment effect' among population-based cases since many were interviewed months after discharge. Study questionnaires may specify talc use before diagnosis, but patients in population-based studies may not always make the distinction between prediagnosis and post-treatment use. In contrast, hospital-based studies ascertain exposure information at the time of discharge and reported talc use is not influenced by postdiagnostic treatment. The reasons why postdiagnostic talc use might be important is that approximately 60% of incident ovarian cancers are stage III or IV (metastatic) disease, which is characterized by a low 5-year survival rate ($\sim$10%). Patients with advanced cancer usually undergo chemotherapy, and possibly debulking surgery whereas early stage disease is usually treated with surgery, whole abdominal radiation, or intraperitoneal radioactive phosphorus. Population-based studies may contain a disproportionately high number of early stage patients owing to their favorable prognosis. Radiation treatment in early stage patients often induces radiation dermatitis in the lower abdomen, a side effect that can be partly alleviated by talc dusting. Other disease symptoms such as bloating from ascites may also prompt talc use. Early stage patients may also subsequently relapse and undergo radiation therapy prompting further talc use.

No published data exist on the specific treatments and medical management of the study participants in these studies and it is unknown whether the above biases are present and to what degree. These alternative explanations, however, for the observed increased risks have not been considered and ruled out as possible explanations for the weak case–control findings. The lack of an increased risk in the prospective Nurses Health cohort study suggests that such biases may be present in the case–control data.

Another factor in the clinical management of ovarian cancer that is relevant to the epidemiology concerns the association in women who have undergone tubal ligation or hysterectomy. These procedures block the environmental contamination of the ovaries, and after excluding women with bilateral oophorectomy, studies that reported on whether the risk was modified by hysterectomy or tubal ligation have not found consistent differences. The interpretation of these data are complicated by evidence indicating that there are other possible hormonal/biological explanations for the reduced risks associated with tubal ligation besides ovarian occlusion. For example, the reduced risk of ovarian cancer associated with hysterectomy could be an artifact resulting from an increased risk of ovarian cancer associated with menopausal hormonal therapy in women with an intact uterus (Glud *et al.*, 2004). An increased risk associated with talc dusting in women who had these surgical procedures could also be biased in the talc studies by the failure to exclude women who underwent unilateral oophorectomy.

Theoretically, the lower risk of ovarian cancer associated with hysterectomy in these women is reduced because 50% of their ovarian tissue was removed.

Talc and other reproductive tract cancers

Genital exposure to talc dust was first hypothesized as not only a possible risk factor for ovarian tumors but also cervical and endometrial cancer. It might be expected that the cervix is at greater risk than the ovaries owing to the build-up of talc particles on the uterine cervix, which serves as a barrier to uterine contamination. This association has not been studied, but such data would be informative.

Therapeutic uses of talc

Cosmetic grade talc is used therapeutically to treat nonmalignant and malignant pulmonary disease. Talc insufflation causes adhesions between the parietal and visceral pleura, and is used in the treatment of bronchopleural fistulas, malignant pleural effusions, and pneumothorax (a collapse of the lung from changes in intrapleural pressure in the chest cavity). The procedure involves the application of chemical agents such as cosmetic grade talc into the pleural space, causing a pleuritis that seals the air leak. The use of carcinogens for medical treatment is not uncommon (e.g. tamoxifen); however, talc pleurodesis has been used as an effective treatment for several decades without concerns about its carcinogenic potential. Talc slurry is directly applied to the pulmonary pleura in concentrations equivalent to experimentally injected doses in animals on a per weight basis. If human bronchial or pleural tissue were treated with 5 g of asbestos instead of talc, it might be reasonably hypothesized that the treatment would significantly increase the rate of mesothelioma or lung cancer in these patients. No case reports, however, exist of lung or pleural cancer following pulmonary pleurodesis.

The safety of talc pleurodesis has been clinically recognized anecdotally for many decades but also supported by clinical studies. In a group of 70 patients medically treated with talc pleurodesis, none developed subsequent malignancies after follow-up for outcomes (Honma *et al.*, 1963). In 99 patients undergoing thoroscopy and asbestos-free talc pleurodesis for spontaneous pneumothorax between 1954 and 1964 (Lange *et al.*, 1988), none developed malignant mesothelioma as of 1985. In 210 patients treated with talc (or kaolin) primarily for pneumothorax between 1956 and 1960, there were no reported cases of mesothelioma after 15–40 years follow-up (Anonymous, 1979), and no excess number of lung cancers. The mean talc particle size and exact method of application may vary between treatment centers (Ferrer *et al.*, 2001), but the pleurodesis studies are consistent with animal experiments that found a lack of tumor induction following pleural implantation of talc (Wagner *et al.*, 1975).

Talc pleurodesis is also used palliatively for the treatment of malignant pleural effusions in patients with advanced breast, lung and other cancers. As life expectancy is limited in patients treated for malignant pleural effusions, the long-term carcinogenic potential of talc pleurodesis is not a significant medical concern, particularly as many of these patients suffer from recurrent malignant pleural effusions. A meta-analysis of 36 randomized, controlled trials with 1499 participants found no evidence that talc pleurodesis for malignant pleural effusions increased short-term mortality relative to controls (Shaw and Agarwal, 2004). As the latency, however, for asbestos-induced malignancies can be lengthy, these clinical findings are less relevant than the pneumothorax data with regard to talc carcinogenicity.

Pleural growth alterations have not been found in tissue specimens obtained from talc-treated patients with malignant and benign pleural effusions (Krismann *et al.*, 1998). Therapeutic concentrations of talc significantly increased apoptosis in human malignant mesothelioma cell lines relative to control cells. No apoptotic effect was found in normal pleural mesothelioma cells (Nasreen *et al.*, 2000).

Heterogeneity in the talc-dusting and ovarian cancer associations

A sensitivity analysis of the perineal dusting studies revealed interesting differences by study design. The summary odds ratio was 1.19 (95% CI: 0.99–1.41) for hospital-based studies and 1.38 (95% CI: 1.25–1.52) for population-based studies. Although traditional dogma suggests that population-based studies are less biased, we have noted that because of a poor prognosis, women enrolled in population-based studies after hospital discharge are more likely to be early stage cases with a history of radiation and treatment for skin irritation, or may have had the opportunity to become more familiar with known and suggested risk factors. In addition, many of the studies of perineal dusting and ovarian cancer included information on dose of talc exposure in terms of duration, frequency and cumulative use. Few, however, found a positive dose–response relationship and an inverse relationship was found in some.

Conclusion

The causes of ovarian cancer are poorly understood but ongoing research will likely uncover important genetic determinants of this disease. In this review, we have discussed that the findings on perineal dusting powders in case–control studies of ovarian cancer are only part of a larger body of relevant literature and perspectives that have not been adequately considered with regard to talc

and ovarian cancer. It may be argued that the overall null findings associated with talc-dusted diaphragms and condom use is more convincing evidence for a lack of a carcinogenic effect, especially given the lack of an established correlation between perineal dusting frequency and ovarian tissue talc concentrations and the lack of a consistent dose–response relationship with ovarian cancer risk. The absence of mesotheliomas in patients treated with therapeutic concentrations would appear to demonstrate a high degree of safety.

The biological rationale for talc carcinogenicity has been misunderstood in terms of its chemical and physical properties, and other suggested mechanisms such as inflammation have not been supported by epidemiologic data. Talc is not fibrous and not genotoxic (Endocapron *et al.*, 1993), and lifetime whole body exposure experiments in female laboratory rats found that ovarian tissue was not contaminated with talc and that ovarian tumor incidence was not increased (Boorman and Seely, 1995).

In addition, inhaled talc in mining and milling operations is not associated with increased pulmonary tumors. International Agency for Research on Cancer classified inhaled talc that does not contain asbestos fibers as a group 3 carcinogen (e.g. inadequate evidence in humans), and the likelihood that talc could selectively induce ovarian cancer and not lung cancer, and at exposure concentrations presumably orders of magnitude lower than that in occupational settings needs to be weighed. We suggest that future research efforts in this area should include determining the validity and reliability of reported perineal talc exposure from dusting and other sources, more detailed assessment of historical usage patterns, determining the influences of disease symptomology and treatment on reported talc use, and determining the risk for other female reproductive tract cancers.

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